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New tricyclic thiochromenone derivatives as metabotropic glutamate receptor-1 (mGluR1) antagonists useful for treating e.g. hemorrhagic stroke and atherosclerosis, especially pain or neurodegenerative diseases

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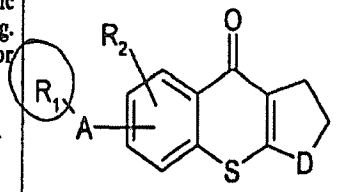
B(6-B2, 14-A1, 14-A2, 14-C1, 14-E5, 14-E12, 14-F2D1, 14-F4, 14-F7, 14-F8, 14-F10, 14-G2D, 14-H1, 14-J1A, 14-J1B, 14-J5, 14-J7, 14-L6, 14-M1, 14-N1, 14-N16, 14-S1, 14-S4) .12



(I)

R_1 - OH reactant

4NOVELTY

Tricyclic thiochromenone derivatives (I) are new.

DETAILED DESCRIPTION

Thiochromenones of formula (I) and their salts, hydrates and/or solvates are new;

R_1 = (i) 6-10C aryl or 5-10 membered heteroaryl (both optionally substituted (os) by one or more of halo, CHO, $CONH_2$, CN, OH, OCF_3, NO_2, NR_3R_4, tetrazolyl or alkoxycarbonyl; or alkyl, alkoxy, 1-6C acyl or alkylthio (all os by OH, morpholinyl, 1-6C acyloxy or halo)); (ii) 3-12 membered carbocyclyl or 4-2 membered heterocyclyl (both os by one or more of alkyl, alkoxy, 1-6C acyl, alkoxycarbonyl or oxo); or (iii) R_5-E-;

A = direct bond, O, S, NR_6, CO, SO, SO_2, SO_2O, $CONR_7$, SO_2NR_8, OSO_2, NR_9CO, $NR_{10}SO_2$, $R_{11}SO_2O$, $NR_{12}SO_2NR_{13}$ or

$NR_{15}CONR_{15}$; or R_1A- = H or NH_2; R_3, R_4 = H, alkyl or 1-6C acyl;

E = optionally unsaturated 1-10C alkanediyl;

R_5 = H, $CONH_2$, halo, OH, NO_2, CF_3, NH_2, mono- or dialkylamino, alkoxy, 6-10C aryl, 5-10 membered heteroaryl or 4-10 membered heterocyclyl (os by oxo and/or alkyl and optionally benzo-fused), where aryl, heteroaryl and benzo groups are os by halo, CN, CF_3, OCF_3, NO_2 or alkyl;

R_6 - R_{15} = 3-8C cycloalkyl or optionally unsaturated alkyl (os by OH, phenyl (os by halo or 1-4C alkyl), alkoxy, alkoxycarbonyl or cycloalkyl);

R_6, R_7, R_9 - R_{12}, R_{14}, R_{15} = H;

R_2 = H, halo, or alkyl or alkoxy (both os by 1 or 2 of OH, alkoxy or mono- or dialkylamino);

D = 3-10C hydrocarbylene (os by F).

Alkyl moieties have 1-6C unless specified otherwise.

Provided that:

(1) the -R_1A- group is in the 2- or 3-position of the thiochromenone ring; and

(2) the compound 2-chloro-6,7,8,9,10,10a-hexahydro-cyclohepta(b)thiochromen-11(5aH)-one is excluded.

ACTIVITY

Neuroprotective; Cerebroprotective; Immunosuppressive; Anticonvulsant; Antiarteriosclerotic; Antidepressant; Nootropic; Antiparkinsonian; Virucide; Antibacterial; Tranquilizer; Neuroleptic; Antidiabetic; Antiemetic; Anorectic; Antiaddictive; Analgesic.

MECHANISM OF ACTION

Metabotropic Glutamate Receptor-1 (mGluR1 receptor) Antagonist.

In receptor binding assays using CHO cells expressing the mGluR1 receptor, 3-ethyl-6-(1H-tetrazol-5-yl)-1,2,3,4-tetrahydro-9H-thioxanthen-9-one (Ia) had an IC_{50} of 9 nM.

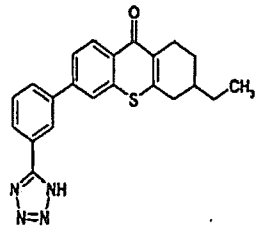
USE

(I) are used as medicaments (claimed), useful for the treatment and/or prophylaxis of neuronal damage diseases or diseases associated with disorders of the glutamatergic system in the central and peripheral nervous system, specifically: (i) neuronal damage associated with ischemic, thrombotic, thrombo-embolic or hemorrhagic stroke, direct or indirect cerebral-cranial injury or post-operative cerebral ischemia; (ii) primary or secondary cerebral

disorders, e.g. associated with cerebral vasospasm, hypoxia/anoxia, preinatal asphyxia, autoimmune, metabolic or organ diseases, convulsions, atherosclerosis or arteriosclerosis; (iii) chronic or psychiatric disorders such as depression, neurodegenerative diseases (e.g. Alzheimer's disease, Parkinson's disease or Huntington's disease, multiple sclerosis, amyotropic lateral sclerosis, neurodegeneration due to viral or bacterial infections or multi-infarct dementia; (iv) dementia of various origins, cerebral insufficiency in the elderly, memory disorders, bone marrow injury, anxiety states, drug-induced Parkinsonian syndrome, psychosis (e.g. schizophrenia), cerebral edema, neuronal damage after hypoglycemia, emesis, nausea, obesity, substance abuse and withdrawal symptoms, CNS-mediated spasms, sedation or movement disorders; or (v) acute and/or chronic pain, especially cancer-induced pain or chronic neuropathic pain. (I) are especially used for the treatment and/or prophylaxis of pain or neurodegenerative diseases (claimed).

SPECIFIC COMPOUNDS

165 Compounds (I) are disclosed, e.g. 3-ethyl-6-(1H-tetrazol-5-yl)-1,2,3,4-tetrahydro-9H-thioxanthen-9-one (Ia).



(Ia)

ADMINISTRATION

Dosage is 0.001-10 mg/kg, preferably 0.005-3 mg/kg in the case of oral administration. (I) are preferably administered orally, parenterally or transdermally, although inhalative or topical administration is also possible.

EXAMPLE

A mixture of 0.5 g 3-ethyl-9-oxo-2,3,4,9-tetrahydro-1H-thioxanthene-6-carbonitrile, 0.51 g triethylammonium hydrochloride

(con't)

and 0.24 g sodium azide was stirred in toluene overnight at 100 °C, cooled, stirred with water and toluene, acidified to pH 3 with hydrochloric acid and further stirred. The obtained solid was filtered off, washed with water, dried and recrystallized from cyclohexane/ethyl acetate to give 3-ethyl-6-(1H-tetrazol-5-yl)-1,2,3,4-tetrahydro-9H-xanthen-9-one (Ia; 290 mg; 50%).

DEFINITIONS

Preferred Definitions:

R_1 = (i) phenyl or 5- or 6-membered heteroaryl (both os by 1 or 2 of halo, CN or 1-3C alkyl); or (ii) 5-7 membered heterocyclyl (os by one or more of 1-3C alkyl or oxo);

A = direct bond, NR_6, SO_2NR_8 or NR_9CO;

R_6, R_8, R_9 = optionally unsaturated 1-3C alkyl (os by 1 or 2 of OH or OMe) or H;

R_2 = H;

D = $(CH_2)_m$-$CR_{16}R_{17}$-$(CH_2)_n$ (having a total of 3-6C);

m, n = 0-2;

R_{16}, R_{17} = H or 1-3C alkyl;

$CR_{16}R_{17}$ = 3-6C cycloalkylidene;

The -R_1A- group is in the 3-position.

TECHNOLOGY FOCUS

Organic Chemistry - Preparation: (I) are generally prepared by introducing and/or modifying the group -AR_1. Typically a corresponding halo compound having -AR_1 replaced by Br or Cl is reacted with:

(i) a boron compound of formula R_{19}-$BR_{20}R_{21}$ (III) in a solvent in presence of a catalyst (preferably under Suzuki coupling conditions) to give (I; -AR_1 = R_{19});

(ii) a heterocyclic compound of formula R_{22}-H (IV) in a solvent to give (I; -AR_1 = R_{22}); or

(iii) an active hydrogen compound of formula R_1-G-H (V) in a solvent in presence of a catalyst to give (I; A = G).

R_{19} = as for R_1 (i);

R_{20}, R_{21} = OH;

$BR_{20}R_{21}$ = 3,3,4,4-tetramethyl-1-bora-2,5-dioxacyclopentane;

R_{22} = N-bonded 4-12 membered heterocyclyl (os as in R_1 (ii));

G = O, S or NR_6.

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